Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-6 and 11-16 are pending in the application, with claims 1 and 11 being the independent claims. Claim 11 is herein amended. This change is believed to introduce no new matter, and its entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Introductory Comments

The Applicants would like to point out that the Examiner has made rejections under 35 U.S.C. § 112, for lack of enablement and written description, in copending Application No. 09/500,991, which rejections are nearly identical to those in the currently pending application. These rejections were withdrawn in light of the arguments made in an Appeal Brief filed on August 30, 2006. The arguments made in the following remarks closely mirror those of the aforementioned Appeal Brief. The Applicants respectfully request that the Examiner consider his reasoning for the withdrawal of the rejections in copending Application No. 09/500,991, and withdraw the rejections in the currently pending case based upon the same arguments and rationale.

II. Rejections under 35 U.S.C. § 112

A. Enablement

Claims 1-5 and 11-15 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. (May 2, 2006 Office Action, page 2). Applicants respectfully traverse this rejection.

According to the Examiner:

> [T]he nature and breadth of the claims encompass any method for identifying a test compound that inhibits the proteolytic activity of a separase using any substrate peptide comprising an amino acid sequence EXXR, wherein X is any amino acid. The examiner takes the position that these separase substrates containing EXXR encompass any peptide comprising any number of amino acid residues including modified and non-naturally occurring amino acid residues.

(May 2, 2006 Office Action, page 2)

The Applicants respectfully submit that the Examiner has ignored the claim limitation requiring that the separase substrate is "*capable of being cleaved by the active separase*". Thus, contrary to the Examiner's assertion, the claims do not encompass methods that involve the use of *any* peptide comprising the amino acid sequence EXXR, but are limited to a peptide capable of being cleaved by separase. As explained in Applicants' previous replies and further elaborated below, a person of ordinary skill in the art would have been able to easily determine through routine experimentation which peptides comprising the amino acid sequence EXXR are capable of being cleaved by active separase. (*See, e.g.*, Reply Under 35 U.S.C. § 1.111, filed on February 9, 2006, pages 4-7).

The Examiner next presented comments regarding the length and composition of the separase substrates used in the practice of the claimed methods. In particular, the Examiner stated that:

> The specification does not provide any guidance or prediction on how the length or the composition of the peptide containing EXXR would affect the ability of the separase to recognize and hydrolyzes [sic] the peptide. The specification does not provide any indication where EXXR should be in relation to the N- or C-terminal of the peptide which will enable the separase to recognize and hydrolyze the peptide. It is not clear from the specification if large peptide comprising EXXR would be hydrolyzed by separase since the specification discloses that small peptides consisting of SEQ ID NO:9, SEQ ID NO: 11, or SEQ ID NO: 12 were found to be separase substrates.

(May 2, 2006 Office Action, pages 2-3).

The Applicants respectfully submit that this argument does not establish a *prima facie* case of lack of enablement. According to the MPEP, in order to establish a *prima facie* case of lack of enablement, the Examiner must "give reasons for the uncertainty of the enablement." M.P.E.P. § 2164.04. The Examiner here has not presented any evidence or line of reasoning to suggest that the length of a peptide containing the separase cleavage motif EXXR, or the position of the EXXR motif relative to the N- and C-termini of the peptide, would influence the peptide's ability to be cleaved by separase. In addition, the Examiner has not presented any evidence to suggest that a person of ordinary skill in the art would have had any difficulty in ascertaining the appropriate sizes of EXXR-containing peptides that could be used in the practice of the claimed methods. Furthermore, the Examiner has not presented any evidence to suggest that a person of ordinary skill in the art would have had difficulty in determining an appropriate position for the EXXR motif relative to the N- and C-termini of a peptide such that it could be recognized and cleaved by a separase. As discussed above and in

Applicants' previous replies, a person of ordinary skill in the art, at the time of filing of the present application, would be able to make and test a wide variety of polypeptide substrates for their ability to be cleaved by separase. (*See, e.g.*, Supplemental Reply filed on June 14, 2005, pages 5-7). Additionally, in a previously filed reply, the Applicants discussed two exemplary references demonstrating that methods of screening for protease substrates were known in the art. (*See* Reply Under 35 U.S.C. § 1.111, filed on February 9, 2006, pages 4-5, citing Smith *et al.* and Cryns *et al.*). The Applicants argued that the methods disclosed by Smith *et al.* and Cryns *et al.* could be used to identify separase substrates for use with the currently claimed methods. The Examiner has not presented any line of reasoning or evidence to contradict this argument. In response, the Examiner stated:

> While the cited references of Smith et al. and Cryns et al. describe general methods for searching and screening for protease substrates, the prior art does not provide guidance or prediction on whether any peptide comprising EXXR and any number of amino acid residues including modified and non-naturally occurring amino acid residues would be hydrolyzed by separase.

(May 2, 2006 Office Action, page 3).

Although the Examiner acknowledged that methods of screening for protease substrates were generally known in the art, the Examiner has failed to explain why methods such as those described in Smith *et al.* and Cryns *et al.* could not be used to identify separase substrates for use with the currently claimed methods. The Examiner stated that the prior art did not provide "guidance" or "prediction" as to whether a given peptide comprising the EXXR motif could be cleaved by separase. The Applicants argue that such specific guidance is not necessary, as the prior art provided methods to

determine whether any given peptide could be used as a separase substrate in the methods described in the currently pending application.

With regard to the Examiner's statement that "[i]t is not clear from the specification if large peptides comprising EXXR would be hydrolyzed by separase . . .," the Applicants would like to point out that the specification contains an Example in which a full-length, myc-tagged SCC1 (which contains an EXXR motif) is cleaved by separase. (*See, e.g.*, Example 1, pages 18-20, and Fig. 1, demonstrating the cleavage of a Myc-tagged SCC1 protein). Thus, contrary to the Examiner's assertion, the specification provides clear evidence that large peptides such as full-length proteins containing the EXXR motif are capable of being cleaved by separase.

Finally, with respect to enablement, the Examiner stated that:

> The Examiner takes the position that trial and error experimentation used for searching and screening for specific peptides comprising EXXR, where such peptides are not limited by amino acid composition and number of residues, must be performed to ascertain which peptides are substrates for separase. In absence of any guidance and prediction from the specification and the art, this experimentation is undue and is outside the realm of routine experimentation.

(May 2, 2006 Office Action, page 3).

The Examiner has not presented any evidence or reasoning to support the conclusion that the amount of experimentation required to identify separase substrates would be "undue" from the perspective of a person of ordinary skill in the art. The Applicants maintain the position that screening for EXXR containing peptides for use as separase substrates in the currently claimed methods would have been a matter of routine experimentation. For Example, as noted in Applicants' previous replies:

1. Techniques for producing *thousands* of peptides having different amino acid sequences were routine in the art at the time of the effective filing date of the present application (*see* Supplemental Reply filed on June 14, 2005, pages 5-6). Thus a skilled person could have easily generated a multitude of EXXR-containing peptides of varying lengths and amino acid compositions that could then have been tested for their ability to be cleaved by active separase;

2. The specification teaches methods that can be used to screen numerous peptides for their ability to be cleaved by separase (*see* Supplemental Reply filed on June 14, 2005, pages 6-7). It follows that a skilled person could have easily distinguished EXXR-containing peptides that are capable of being cleaved by active separase from those that are not cleaved;

3. Smith *et al.* demonstrated a protease substrate screening method that uses bacteriophage-based peptide display libraries (*see* Reply Under 37 C.F.R. § 1.111 filed on February 9, 2006, page 5); and

4. Cryns *et al.* set forth a method that was used to identify caspase substrates using labeled protein pools that had been transcribed/translated *in vitro* (*see* Reply Under 37 C.F.R. § 1.111 filed on February 9, 2006, page 5).

Thus, taken together, the teachings of the specification and the evidence of record strongly indicates that screening for and identifying EXXR-containing peptides that are capable of being cleaved by active separase would have been routine to persons of

ordinary skill in the art. In contrast, no evidence has been put forth to suggest the opposite.

In view of the foregoing remarks, the Applicants respectfully submit that the Examiner has not established a *prima facie* case of lack of enablement. Accordingly, Applicants respectfully request that the enablement rejection be reconsidered and withdrawn.

B. Written Description

Claims 1-5 and 11-15 were rejected under 35 U.S.C. § 112, first paragraph, for lack of adequate written description. (May 2, 2006 Office Action, page 3). Applicants respectfully traverse this rejection.

In support of the written description rejection, the Examiner stated that:

> [T]he claims are genus claims that encompass a genus of peptides of any amino acid sequence, structure, and biological function comprising the amino acid sequence EXXR, where X is any amino acid, or comprising the amino acid sequence of SEQ ID NO: 9, SEQ ID NO: 11, and SEQ ID NO: 12. The genus of peptides containing EXXR, SEQ ID NO: 9, SEQ ID NO: 11, or SEQ ID NO: 12 encompass any peptide comprising any number of amino acid residues including modified and non-naturally occurring amino acid residues.

(May 2, 2006 Office Action, pages 3-4).

The Examiner has the initial burden of establishing a reasonable basis for challenging the adequacy of the written description for a claimed invention. *See Wertheim*, 541 F.2d at 263, 191 U.S.P.Q. at 97. The Applicants submit that the Examiner has merely presented conclusory arguments that are unsupported by the evidence of record and fail to take into account the current state of the law regarding

written description or the level of skill in the art. Thus, the Examiner's burden has not been met.

When assessing the adequacy of written description provided for a particular claimed invention, it is necessary to consider the level of skill in the art. Applicants submit that the Examiner has failed to fully consider the level of skill in the art at the time of filing of the currently pending application. As articulated recently by the Federal Circuit:

> The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented advance is novel in relation to the state of the science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science.

Capon, 418 F.3d at 1357, 76 U.S.P.Q.2d at 1084.

The level of skill and knowledge in the art relating to the production and use of proteolytic substrates was extremely high at the time of the effective filing date of the present application. For example, having knowledge of a particular cleavage motif (such as EXXR), a skilled person would simply identify and/or isolate naturally occurring peptides or polypeptides having the cleavage motif, or alternatively, produce synthetic peptides that contain the motif. The isolation of naturally occurring peptides or polypeptides having a particular cleavage motif could have easily been accomplished using genetic screening methods.

The level of skill in the art of producing synthetic proteolytic substrates containing a particular cleavage motif was likewise extremely high. For example, at the time of the effective filing date of the present application, techniques for producing

thousands of peptides having predetermined amino acid sequences were routine in the art. Such techniques include, *e.g.*, the production of recombinant nucleic acid molecules that encode peptides containing a protease cleavage motif, and the direct production of multiple peptides that include the cleavage motif. (*See, e.g.*, Rodda, "Synthesis of Multiple Peptides on Plastic Pins," in *Current Protocols in Protein Science*, John Wiley & Sons, Inc. (1997), Exhibit 3). Thus, the level of skill in the art of producing multiple peptides and polypeptide sequences, including those containing a particular proteolytic cleavage motif such as EXXR, was very high. The Examiner has not presented any evidence or line of reasoning to refute this assertion. Thus, the Examiner has ignored the advanced state of the art and the ability of persons of ordinary skill to make, test and use a wide range of proteolytic substrates using routine biological techniques. Moreover, the Examiner has not provided any explanation or evidence to suggest that a person of ordinary skill in the art, in view of the knowledge available in the art, would have been unable to recognize members of the genus of separin substrates defined in the claims without resorting to burdensome experimentation.

Furthermore, the Examiner stated:

> The specification does not disclose how the length or the composition of the peptide containing EXXR would affect the ability of the separase to recognize and hydrolyzes the peptide. The specification does not disclose where the EXXR should be in relation to the N- or C-terminal of the peptide which will enable the separase to recognize and hydrolyze the peptide. It is not clear from the specification if large peptides comprising EXXR would be hydrolyzed by separase since the specification discloses that small peptides consisting of SEQ ID NO:9, SEQ ID NO: 11, or SEQ ID NO: 12 were found to be separase substrates.

(May 2, 2006 Office Action, page 4).

Applicants would again like to emphasize that there is no evidence of record to suggest that determining the appropriate size of a separin substrate, the relative orientation of the EXXR sequence, or the appropriate location of the EXXR motif in relation to the N- or C-terminus within the substrate would have entailed anything more than the application of routine techniques. Furthermore, as stated *supra*, the specification contains an Example in which a full-length, myc-tagged SCC1 (which contains an EXXR motif) is cleaved by separase. (*See, e.g.*, Example 1, pages 18-20, and Fig. 1, demonstrating the cleavage of a Myc-tagged SCC1 protein).

In view of the foregoing discussion, Applicants submit that the subject matter of claims 1-6 and 11-16 is more than adequately described and that a *prima facie* case of inadequate written description has not been established with respect to these claims. Thus, Applicants respectfully request that the written description rejection be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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